

## REMARKS

Claims 1-31 are currently pending. Claim 1 has been amended to recite that at least one carrier protein P is Dt and another is Tt and that that amounts are 60 µg/doses and 25 µg/dose, respectively. Support for this amendment can be found on p. 5, ll. 15-36, and p. 8, ll. 12-21.

The applicants thank the Examiner for the professional and useful interview conducted October 24, 2008. The applicants agree with the Interview Summary record prepared by the examiner: predictability and failures in the art with regard to combining antigenic components was discussed, as was the phenomenon of conjugate carrier extinction/suppression (also known as carrier-induced epitopic suppression (CIES)).

### **Rejection pursuant to 35 U.S.C. § 103(a)**

Claims 1 – 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu, *et al.*, (Infection and Immunity, 40(1):245-56, April 1983) (hereinafter “Chu”) in view of European Patent Application No. 0 497 525, May 8, 1992 (the ’525 publication). Applicants respectfully traverse this rejection.

The presently amended claims are directed to compositions comprising two or more protein carrier – *S. pneumoniae* polysaccharide conjugates in which there are at least two different protein carriers, at least one of which is the diphtheria toxoid (Dt) and another is the tetanus toxoid (Tt). As discussed on pages 3-5 of the specification, the applicants were the first to discover that the phenomenon of CIES could be circumvented in *S. pneumococcal* polysaccharide conjugate vaccines by employing two or more different carriers, thereby enabling reduction in the amount of each carrier protein carrier and, correspondingly, reducing suppression of the immune response directed toward the *S. pneumoniae* polysaccharide antigens.

In brief, CIES is an immunological phenomenon whereby the immune response directed toward a hapten of a protein-hapten conjugate is suppressed by prior immunization with the protein carrier; the immune response is diverted from the hapten to the protein carrier (*See, e.g.,* Schutze et al., J. Immun. **135**, 2319 (1985) and Peeters et al., Infect. Immun. **59**, 3504 (1991).) The applicants observed (pp. 3-4 of the specification) that in pneumococcal conjugate vaccines based on Dt or Tt as the sole carrier protein co-administered with an *Haemophilus influenzae* type b (Hib) vaccine (PRP-Tt), the anti-Hib antibody response *decreased* as the Tt and Dt loads

*increased*. The applicants discovered that this negative interference effect could be addressed through reduction of the load of a specific protein carrier without sacrificing the amount of conjugated polysaccharide antigen and, concomitantly, the immune response against the polysaccharide. As embodied in the present claims, the applicants accomplished this by employing a composition wherein the conjugates are comprised of one of two or more different protein carriers. In this way the amount of polysaccharide is maintained at a high level while the load of each particular protein carrier is reduced by spreading the carrier function among two or more different proteins. The prior art is silent with regard to such a solution, neither teaching or suggesting such an approach.

The ability to reduce specific protein carrier load is also embodied in the present claims: claim 1 recites that at least one protein carrier is Dt present in an amount of less than or equal to 200 µg/dose (claims 1 and 16) or 60 µg (claim 25) and at least one protein is Tt present in an amount of less than or equal to 50 µg/dose (claims 1 and 16) and 20 µg/dose (claim 25).

The prior art provides no teachings, suggestions, or, indeed, recognition that the amount of carrier protein could be controlled in such a manner.

Furthermore, each of the presently pending claims recites that the compositions include both conjugates in which Dt is the carrier protein and conjugates in which Tt is the carrier protein. The applicants respectfully submit that it would have been contrary to the inclinations of those of ordinary skill in the art to combine both such conjugates because those skilled in the art know of the ubiquitous nature of early childhood vaccination with the DTP vaccine. Those of ordinary skill in the art would have recognized that most individuals who would be receiving a pneumococcal vaccine would have been pre-immunized with Dt and Tt. Combined with the Finnish and Israeli studies discussed on pp. 3-4 of the specification showing decreased anti-Hib antibody response with increased Dt and Tt load, one of ordinary skill in the art would likely have avoided combining Dt and Tt as carrier proteins in a single vaccine composition because of the perceived likelihood of inducing CIES. And given the potential for CIES, nothing in the art would have permitted one of ordinary skill in the art to have reasonably predicted that the presently claimed combination would be effective at inducing an adequate immune response against the corresponding conjugated *S. pneumoniae* polysaccharide.

In the present Action the Office takes the position that the applicants have merely selected a combination of known elements from a finite number of possibilities to yield a

composition having predictable properties, concluding that the claims are, therefore, obvious under the *KSR* “obvious to try” standard. The applicants respectfully disagree. First, the applicants take issue with the Office’s interpretation of *KSR* and respectfully submit that it has misconstrued and misapplied *KSR*. With regard to “obvious to try, the Court stated:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1390 (U.S. 2007) (emphasis added). The applicants do not argue that there was market pressure to overcome the problem of CIES and produce an effective *pneumococcal* vaccine (although as explained below, the applicants submit that market pressure and desire existed for such a long time as to be evidence of the non-obviousness of the claimed invention). Rather, the applicants submit that in the present situation the Office has assumed but provided no evidence of (1) a finite number of (2) identified and (3) predictable solutions. The applicants respectfully submit there is no such evidence.

Furthermore, even to posit that there is a finite number of identified and predictable solutions is an indication of hindsight reconstruction of the claimed invention because there is nothing identified in the prior art that suggests that the only way to overcome the problem of CIES and/or produce an effective *pneumococcal* vaccine is simply to find the correct combination of conjugate components or that doing so would be effective. The applicants respectfully submit that focusing only on this approach without such prior art suggestion is an indication of hindsight reconstructions of the present claims.

Second, if the presently claimed compositions were obvious or even obvious to try, the applicants respectfully ask why did it take nearly 100 years from the discovery of conjugate vaccines for the presently claimed compositions to be discovered, particularly in the face of intense pressures to develop vaccines against the widespread and devastating effects of *S. pneumococcal* infection? Such long felt need is evidence of the non-obviousness of the presently claimed compositions.

In addition, one of ordinary skill in the art would not and could not combine any random collection of antigens and expect to observe a safe and useful immunogenic response, which is

essentially what the Office is arguing. The applicants respectfully submit that one could not have known *a priori* whether the presently claimed combination of conjugates would yield the desired results. Simply put, while it would be a routine matter to prepare, test, and use the presently claimed combination, one could not have predicted *a priori* that the combination would yield a composition having sufficient immunogenicity against the desired target. The prior art fails to imbue the ordinary artisan with the predictability in outcome essential in the *KSR* analysis.

While the Office has identified teachings of successful combinations of multiple antigens, those of ordinary skill in the art are also aware of the numerous failures observed when combining antigens. Those of ordinary skill in the art are aware of the hurdles (e.g., those related to negative interference) that can be encountered when combining antigens and that such hurdles would have made it impossible to reasonably predict the results of the present combination of pneumococcal conjugates. Applicants can supply evidence of failures if the Office so desires.

Neither Chu nor the '525 application, alone or in combination, suggest or provide reason to make the presently claimed combinations of conjugates with at least one Dt protein carrier and at least one Tt protein carrier or that the loads of these carriers could be reduced while at the same time while maintaining the immunogenicity against the conjugated *pneumococcal* polysaccharides. Even were one to combine Chu and the '525 application, one would not arrive at the presently claimed compositions as such a combination would not comprise both Tt and Dt carrier proteins. And for the reasons explained above, one would not modify the composition of Chu or the '525 application in a manner that would yield the presently claimed compositions (e.g., employing both Dt and Tt as carriers in a single composition), nor would one have been able to predict the results in so doing.

The thrust of the Office's rejection appears to be that the '525 application teaches a multivalent vaccine and the art recognized the benefits of conjugating the valences to carrier proteins, therefore it would have been obvious to select from known protein carriers to arrive at the presently claimed compositions. But, as previously explained, the presently claimed composition are not merely the combination of conjugated *pneumococcal* polysaccharide valences. Rather, they embody the discovery that *pneumococcal* polysaccharide valences could be conjugated to both Dt and Tt and that the loads of Dt and Tt could be reduced, thereby avoiding the effects of CIES in populations previously sensitized to Dt and Tt via the

ubiquitously administered DTP vaccine. These discoveries are nowhere found or suggested in the cited art.

In view of the foregoing amendments and remarks, the Applicants submit that Chu and the '525 publication do not render obvious the presently pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

**New rejection pursuant to 35 U.S.C. § 103(a)**

Claims 1, 2, 4, 6, 7, and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ahman *et al.* (Pediatr. Infect. Dis. J. 15:134-9, 1996) in view of Anderson *et al.* (J. Pediatr. 128:649-53, 1996). Applicants respectfully traverse this rejection.

The Office relies on Ahman's teaching of a *pneumococcal* conjugate vaccine PncCRM comprising oligosaccharides conjugated to the nontoxic mutant diphtheria toxin CRM197 (abstract and page 135, col. 1, vaccines). The Office cites Anderson for its teaching of a multivalent *pneumococcal* vaccine conjugated to the outer membrane protein complex of *Neisseria meningitides* (abstract and page 650, col. 1-2, vaccines). However, the combination of Ahman and Anderson does not teach, suggest, or provide a reason to make a vaccine composition comprising at least two different kinds of polysaccharide-carrier protein conjugates with at least two different protein carriers, one of which is Dt and another of which is Tt, as currently claimed. Even were one to combine the multivalent vaccines of Ahman and Anderson one would not arrive and the presently claimed compositions because the combination would not comprise both Tt and Dt carriers.

Furthermore, for the reasons stated above, it would not have been obvious to one of ordinary skill in the art to modify the teachings of Ahman and Anderson to arrive at the presently claimed compositions.

Therefore, Applicants submit that Ahman and Anderson do not render obvious the invention of claims 1, 2, 4, 6, 7, and 14. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 1-31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ahman *et al.* (Pediatr. Infect. Dis. J. 15:134-9, 1996) in view of Anderson *et al.* (J. Pediatr. 128:649-53,

1996) as applied to claims 1, 2, 4, 6, 7, and 14 *supra* and further in view of the '525 publication. Applicants respectfully traverse this rejection.

On page 8 of the Office Action, the Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to conjugate each *S. pneumoniae* polysaccharide of the '525 publication to a different carrier protein as taught by the art. But the '525 publication does not teach a vaccine composition containing at least two carrier proteins conjugated to polysaccharides, one carrier of which is Dt and another is Tt. In fact, the '525 publication consistently describes compositions containing a single carrier protein. And as just previously noted, the Ahman and Anderson teachings are not directed to a composition comprising conjugates with at least two different carrier proteins either. This element being absent from the teachings of all three references employed in the present rejection means that combining them would not result in the presently claimed subject matter.

Nor would it have been obvious for one of ordinary skill in the art to have modified the teachings of Ahman and Anderson in view of the '525 application to arrive at the presently claimed compositions for the very same reasons described above.

Therefore, Applicants submit that Ahman, Anderson, and the '525 publication do not render obvious the invention of claims 1-31. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

In light of the above remarks, Applicants submit that the present application is in condition for allowance and respectfully request notice to this effect.

The Examiner is invited to contact Applicants' representative below if any questions arise or he may be of assistance to the Examiner.

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